









Eosinophilic Fasciitis Following Checkpoint Inhibitor Therapy: Four Cases and a Review of Literature

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Key Words. Checkpoint inhibitor • Eosinophilic fasciitis • Immune-related adverse event

ABSTRACT

Background. Checkpoint inhibitor therapy is widely known to cause a number of immune-related adverse events. One rare adverse effect that is emerging is eosinophilic fasciitis, a fibrosing disorder causing inflammatory infiltration of subcutaneous fascia. It is characterized clinically by edema and subsequent induration and tightening of the skin and subcutaneous tissues. The condition is rare, yet at our institutions we have seen four cases in the past 3 years. We describe our 4 cases and review 11 other cases reported in the literature.

Case Presentation. We present four cases of eosinophilic fasciitis following treatment with programmed cell death protein 1 or programmed cell death-ligand 1 blockade. All patients had extremity involvement with characteristic skin changes ranging from peripheral edema to induration, tightening, and joint limitation. The patients had varying degrees of peripheral eosinophilia. In two of our patients, the diagnosis was made by full-thickness skin biopsy showing lymphocytic infiltration

of the subcutaneous fascia, with CD4+ T cells predominating in one case and CD8+ T cells in the other. In the other two cases, the diagnosis was made on the basis of characteristic imaging findings in the context of clinical features consistent with the diagnosis. All four patients were treated with glucocorticoids with varying degrees of success; immunotherapy had to be discontinued in all four. Patients with advanced melanoma who experienced this adverse effect had either a partial response or a complete response to therapy.

Conclusion. Eosinophilic fasciitis can occur as a result of checkpoint inhibitor therapy. Although a tissue diagnosis is the gold standard, imaging studies may facilitate the diagnosis in the presence of consistent clinical features, but a degree of suspicion is key to recognizing the condition early. Therapy requires a collaborative approach by oncology, rheumatology, and dermatology; physical therapy is an important adjunct in treatment. For advanced melanoma, it may be a good prognostic indicator. *The Oncologist* 2020;25:140–149

Implications for Practice: It is important for clinicians to recognize that eosinophilic fasciitis is a potential immune-related adverse event (irAE) as a consequence of immune checkpoint inhibitor therapy. The presentation is quite stereotypical; the diagnosis can be made by imaging in the absence of a full-thickness skin biopsy. Early intervention is important to limit morbidity. This irAE may be a good prognostic sign among patients with melanoma.

INTRODUCTION

Checkpoint inhibitors (CPIs) have changed the landscape of cancer therapeutics. Since the approval of ipilimumab, a cytotoxic T-lymphocyte-associated-protein (CTLA)-4–blocking antibody, for metastatic melanoma in 2011, a number of other CPIs have been approved for a variety of malignancies, including blockers of programmed cell death protein 1 (PD-1) and its ligand PD-L1. Under physiologic conditions, upon T-cell activation,

checkpoints are upregulated and engaged in order to limit immune activation and tissue damage. Checkpoint inhibitors allow T cells to remain active against tumor cells [1]. The persistent activation of T cells has resulted in many well-documented immune-related adverse events (irAEs) affecting multiple organs [2]. In rheumatology, the most common irAEs are arthritis, sicca syndrome, polymyalgia rheumatica, and myositis [3].

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Eosinophilic fasciitis (EF) is a rare fibrosing condition characterized by erythema, edema, and induration of extremities, often, but not always, accompanied by peripheral eosinophilia. It is considered a scleroderma mimic, in that skin tightening is the prominent symptom, but unlike scleroderma, patients with EF do not have sclerodactyly, Raynaud's phenomenon, telangiectasias, or nailfold capillary changes; conversely, patients with scleroderma do not exhibit a "groove sign" or peau d'orange. EF is characterized by inflammatory infiltration, thickening, and fibrosis involving the fascia [4–6]. In the oft-cited criteria set proposed by Pinal-Fernandez in 2014, predicated on the exclusion of systemic sclerosis, the two major criteria for diagnosis are (a) swelling or induration of the skin and subcutaneous tissues and (b) fascial thickening with lymphocytes and macrophages, with or without eosinophilic infiltration on biopsy. If only one major criterion is present, the presence of any two of the following minor criteria can help make the diagnosis: (a) peripheral eosinophilia, (b) hypergammaglobulinemia, (c) muscle weakness, (d) groove sign, and (e) hyperintense fascia on T2-weighted images by magnetic resonance imaging (MRI) [7].

Although EF is quite rare, we have seen four cases of EF following treatment with a PD-1 or PD-L1 inhibitor over a 3-year period, suggesting that PD-1/PD-L1 blockade is a potent trigger of this condition. With the increasing number of indications for CPI therapy, clinicians need to be aware of this entity as a potential irAE, as morbidity can be diminished if recognized early. Here we present our 4 cases and review the additional 11 cases from in the literature.

CASE 1

A 48-year-old man was referred to rheumatology for a chief complaint of leg stiffness. He had received treatment with atezolizumab (1,200 mg every 3 weeks for 13 doses) in combination with erlotinib as part of a trial for a diagnosis of stage IV lung adenocarcinoma. Six months into treatment, he noted tightness and pain in his upper and lower extremities accompanied by leg swelling. Creatine kinase (CK) was initially elevated to 933 U/L but subsequently normalized without intervention over 2 weeks; absolute eosinophil count (AEC) climbed from 700 to 3,500 three months later. Three months after the onset of his symptoms, atezolizumab was discontinued. Five months after the onset of his symptoms, he was referred to rheumatology. Examination revealed thickening of the skin of the forearms and of the legs below the knees that limited mobility at the elbows, wrists, knees, and ankles. A "groove sign" was noted over the left leg (Fig. 1A) and right forearm. MRI of the left tibia showed mild fascial edema (Fig. 2A). A full-thickness skin biopsy showed changes consistent with eosinophilic fasciitis: there was striking expansion of the fascia by collagen, hyaluronic acid, and fibrin accompanied by numerous lymphocytes and plasma cells; significant tissue eosinophilia was not observed. CD3 staining revealed the presence of T lymphocytes, predominantly CD8+ T cells, with a CD4-to-CD8 ratio of 1:5 (Fig. 3). The patient was treated with prednisone 60 mg/day and methotrexate 20 mg weekly. Methotrexate was discontinued after 1 month because of conflict with further chemotherapy. Over the course of 3 years, although punctuated initially with flares of the skin disease



Figure 1. Spectrum of skin findings. **(A):** Patient 1. Groove sign along a superficial vessel, with swelling around the medial malleolus. **(B):** Patient 4. Puffiness of the hands and fingers with limited finger extension. **(C):** Patient 4. Pedal edema most obvious around the lateral malleolus.

requiring intermittent high-dose steroids, his skin eventually started to soften. His malignancy progressed but responded to additional surgery and chemotherapy.

CASE 2

A 71-year-old female was evaluated for myalgias and pitting edema following nivolumab therapy. She had been diagnosed with vulvar melanoma 2 years prior to presentation and underwent a vulvar resection. For her first local recurrence, she received radiation therapy. She was later found to have disease metastatic to lymph nodes and lungs, for which she was started on nivolumab (480 mg monthly × three doses). She had a good response to the treatment, with repeat scans demonstrating shrinkage of some lesions and resolution of others. After her third treatment, she developed myalgias involving the shoulders, thighs, and calves, with a pronounced diurnal variation, accompanied by subjective fevers, and pitting edema in the arms and feet. Nivolumab was held. On presentation to rheumatology, she was given a preliminary diagnosis of either polymyalgia

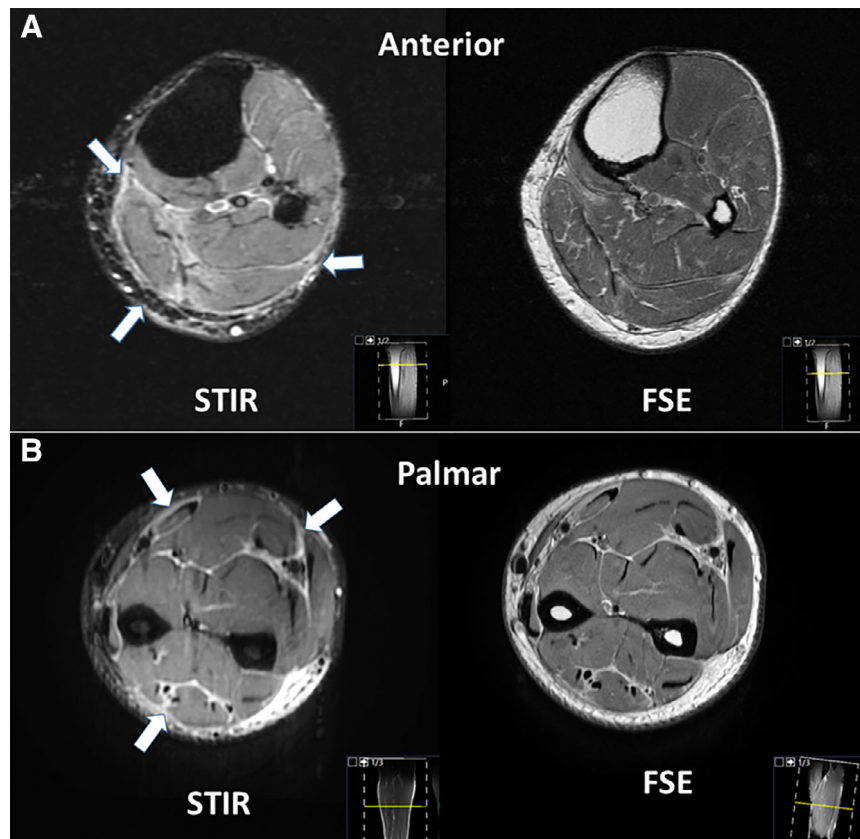


Figure 2. Magnetic resonance imaging findings. **(A):** Patient 1. Axial section through the proximal leg shows fascial edema (arrows in STIR) and preserved muscle bulk in intermediate-weighted FSE sequences. **(B):** Patient 3. Axial section through the mid-forearm shows fascial edema (arrows in STIR) and preserved muscle bulk in intermediate-weighted FSE sequences. Abbreviations: FSE, fast spin echo; STIR, short tau inversion recovery.

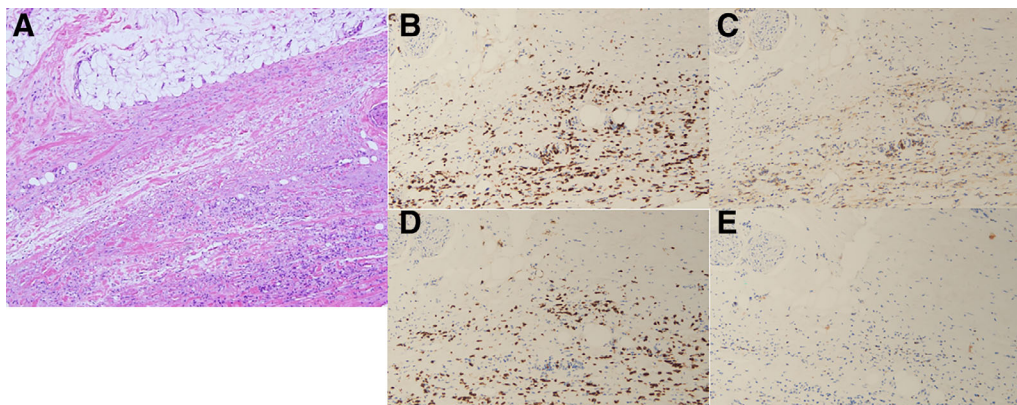


Figure 3. Full-thickness skin biopsy from patient 1. **(A):** Hematoxylin and eosin staining at $\times 400$ showing broad, hyalinized collagen bundles within the fascia with deposition of mucin and a lymphocytic and plasma cell infiltrate. **(B–E):** Immunostains demonstrating CD8+ T-cell predominance ($\times 200$). Lymphocytes are primarily of the T-cell subset as revealed by the extent of immunoreactivity for CD3 **(B)**. The T cells comprise a mixture of CD4+ T cells **(C)** and CD8+ T cells **(D)**, with some cells staining positive for granzyme **(E)**.

rheumatica or relapsing seronegative symmetric synovitis with pitting edema related either to her malignancy or to the nivolumab. She was treated with prednisone 60 mg and infliximab 3 mg/kg initially. On her second visit 1 month later, she was noted to have a taut consistency to her skin in a circumscribed area measuring 3 \times 5 cm on each forearm just proximal to the wrists. Punch biopsy of the skin showed only poikiloderma. By her third visit another month later, the waxiness had extended to involve the forearms

circumferentially, with tethering and a “woody” texture. Prior to her first visit with rheumatology, her AEC peaked at 2,400; CK was normal. A full-thickness skin biopsy confirmed the diagnosis of eosinophilic fasciitis, with an inflammatory fibrosing reaction involving the subcutaneous tissue, fascia, and skeletal muscle. The inflammatory cell infiltrate consisted of lymphocytes, plasma cells, and eosinophils. CD3 staining confirmed the presence of T lymphocytes, most of which were CD4+, with a CD4-to-CD8 ratio of roughly 4:1 (Fig. 4).

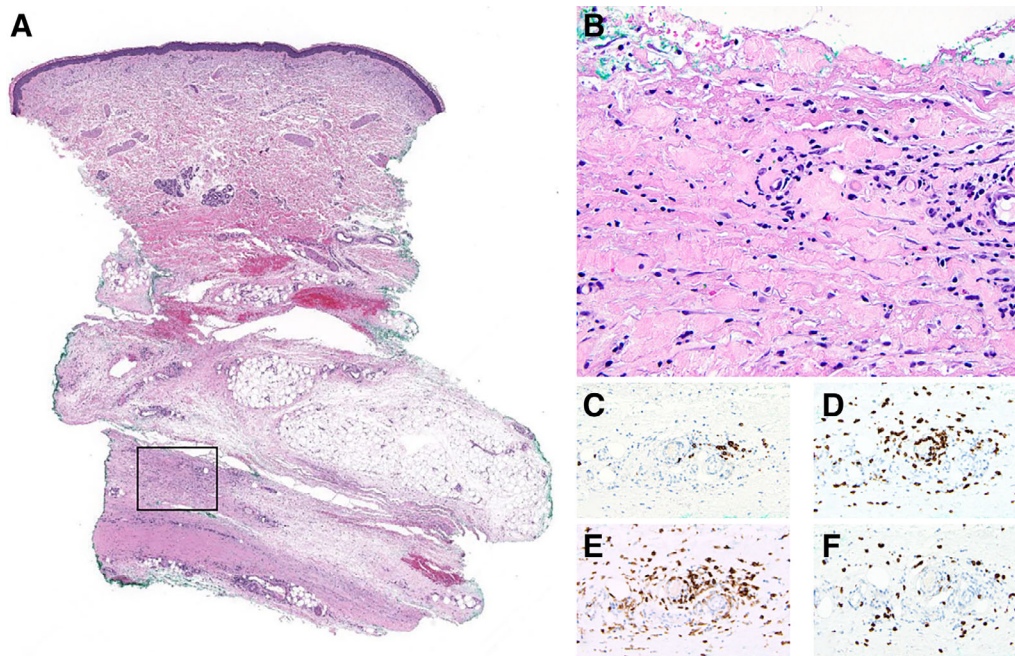


Figure 4. Full-thickness skin biopsy from patient 2. **(A):** Fibrosing stromal changes with predominant involvement of deep subcutaneous tissue and fascia is appreciated at low magnification (hematoxylin and eosin [H&E], $\times 10$; square indicating area seen at higher magnification in **(B)**). **(B):** Inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils is seen in perivascular and interstitial pattern on a background of sclerosis and fibrinoid degenerative changes (H&E, $\times 400$). **(C):** CD20 immunostain highlights few B cells. **(D):** CD3 immunostain highlights the lymphocytic infiltrate that corresponds predominantly to T cells. **(E):** Most T cells are CD4+. CD4 also highlights occasional dendritic cells and histiocytes. **(F):** CD8+ T cells are also present. **(C–F $\times 200$)**

The patient continued on prednisone 60 mg/day and was started on methotrexate 15 mg weekly, to which she had a good response. Twelve months after her last dose of nivolumab, her scans reveal no evidence of metastatic melanoma. Methotrexate was discontinued because of medication intolerance, but the patient remains on 5 mg of prednisone, which has halted the progression of skin changes.

CASE 3

A 43-year-old male was diagnosed with metastatic melanoma. He received pembrolizumab at 2 mg/kg (200 mg) every 3 weeks. Fifteen months (20 doses) later, he developed subjective tightness and swelling of the forearms with some loss of mobility at the wrists, followed later by discomfort in the back of the knees with foot dorsiflexion. He was unable to do pushups, squats, or jumps because of forearm, wrist, and leg tightness. Upon evaluation by rheumatology 4 weeks later, he was noted to have limited wrist mobility bilaterally and swelling of the volar aspect of the forearms. The skin had a normal appearance and the fascia was not “woody.” His CK was normal, and AEC was 700. MRI of the right forearm showed mild tenosynovitis in the flexor and extensor compartments, with fascial edema and relatively maintained muscle signal (Fig. 2B). Pembrolizumab, to which his cancer had had a complete response, was held. Prednisone was initiated at 40 mg daily and subsequently increased to 40 mg twice daily, without a significant response. Mycophenolate mofetil (MMF) 3 grams per day was added to his regimen, and prednisone was tapered. Two months after MMF

initiation, while on prednisone 25 mg daily, the patient began to note significant clinical improvement.

CASE 4

A 70-year-old male with a history of multiple sclerosis on weekly interferon beta 1a was diagnosed with metastatic melanoma and received treatment with pembrolizumab 2 mg/kg (140 mg every 3 weeks for 13 doses), to which his cancer had a partial response. Eight months after initiation of treatment, he developed right foot and right hand swelling and his monitoring abdominal computed tomography scan showed mild edema of the posterior subcutaneous abdominopelvic tissues. AEC was 2,300. Following a 6-day solumedrol taper starting at 24 mg, his arm and leg swelling improved by about 75%. Four months later, he developed explosive onset diffuse swelling of the hands, arms, feet, and legs accompanied by a profound fatigue and weight loss. He received treatment with 60 mg of prednisone and the anti-immunoglobulin E (IgE) agent omalizumab (IgE level 229 kU/L; upper limit of normal 214 kU/L), which resulted in minor improvement. Upon presentation to rheumatology, the patient’s extremities were tight and woody distally > proximally. He had some puckering of the skin of the upper arms and a positive groove sign. He had limited finger extension and significant ankle edema (Fig. 1B, 1C), with involvement of the skin of the lower abdominal wall. He had limited range of motion in the shoulders, elbows, wrists, fingers, knees, and ankles. Prednisone was increased to 40 mg twice daily, and methotrexate was added to his regimen. The patient’s condition progressed despite maximal methotrexate

Table 1. Cases of eosinophilic fasciitis following checkpoint inhibitor therapy: clinical characteristics and malignancy status

Patient no.	Reference	Sex	Age, years	Malignancy	Checkpoint inhibitor	Onset, months	Cancer status	Checkpoint discontinued
1	Current paper	M	48	Stage IV pulmonary adenocarcinoma	Atezolizumab 1,200 mg every 3 weeks × 13	6	Progression	Yes
2	Current paper	F	71	Metastatic melanoma	Nivolumab 480 mg monthly × 3	3	Complete response	Yes
3	Current paper	M	43	Metastatic melanoma	Pembrolizumab 200 mg every 3 weeks × 20	15	Complete response	Yes
4	Current paper	M	70	Metastatic melanoma	Pembrolizumab 140 mg every 3 weeks × 13	8	Partial response	Yes
5	Khoja et al., 2016	F	51	Metastatic melanoma	Pembrolizumab	18	Complete response	Yes
6	Lidar et al., 2018	F	53	Melanoma	Pembrolizumab	8	Complete response	Yes
7	Andrés-Lencina et al., 2018	M	65	Stage IV bladder cancer	Nivolumab + ipilimumab × 3 months, then nivolumab alone	16	Progression	Yes
8	Le Tallec et al., 2019	F	56	Stage IV pulmonary adenocarcinoma	Nivolumab	9	Stable disease	Not reported
9	Toussaint et al., 2019	F	77	Metastatic melanoma	Pembrolizumab	22	Complete response	Yes
10	Rischin et al., 2018	M	55	Metastatic melanoma	Nivolumab	24	Complete response	Yes
11	Parker et al., 2018	F	43	Metastatic melanoma	Nivolumab	15	Complete response	Not reported
12	Daoussis et al., 2017	M	64	Renal cell carcinoma	Nivolumab	10	Not reported	Not reported
13	Narvaez et al., 2018	F	67	Metastatic renal cell carcinoma	Pembrolizumab	2	Progression	Yes due to cancer progression
14	Narvaez et al., 2018	M	56	Metastatic urothelial carcinoma	Avelumab	1.5	Progression	Yes due to cancer progression
15	Bronstein et al., 2011	F	74	Melanoma	Ipilimumab	14	Complete response	Not reported

Abbreviations: F, female; M, male.

dosing at 25 mg weekly. The patient responded but flared when prednisone was tapered to 30 mg twice daily. His multiple sclerosis precluded treatment with tumor necrosis factor and interleukin (IL)-6 blockers, so the CTLA-4 agonist abatacept was added to his regimen.

DATA REVIEW

There are 11 reported cases of fasciitis resulting from CPI therapy, although they are variably labeled: 5 are described as “eosinophilic fasciitis,” [8–12] 1 “lymphocytic fasciitis,” with only mild eosinophilia and without an eosinophilic infiltrate within the fascia on biopsy [13], 4 “myofasciitis” (fasciitis with muscle involvement) [14–16], and 1 “asymptomatic fasciitis.” [17].

Table 1 describes our 4 newly reported cases and summarizes the 11 cases from the literature. Nine had metastatic melanoma, and two each had renal cell carcinoma, urothelial

cancers, and non-small cell lung cancer, reflecting the Food and Drug Administration (FDA)-approved indications for CPI. Thirteen cases occurred after treatment with a PD-1 blocker, one of whom received initial combination therapy with a CTLA-4 blocker in addition to the PD-1 blockade. One case occurred after PD-L1 blockade. The case of asymptomatic abdominal fasciitis, published in 2011, is the only one to occur following treatment with a CTLA-4 blocker alone [17]; indeed, the first PD-1 blocker was not FDA approved until 2014. Onset of symptoms was anywhere from 1.5 to 24 months after initiation of treatment. CPI treatment was discontinued in 11 cases: in 2 patients because of cancer progression and in 9 cases because of the irAE. The status of CPI treatment is not reported in four cases. Most patients were treated with steroids; eight were treated with methotrexate, one with mycophenolate mofetil, and one with abatacept (Table 2). With regard to cancer status, all nine patients with metastatic melanoma had either a complete response ($n = 8$) or a partial response ($n = 1$). In

Table 2. Laboratory, imaging, histopathology results, and therapy

Patient no.	Reference	Presentation and physical exam findings	CK, U/L	Peak absolute eosinophil count, per μ L	Imaging	Biopsy	Treatment
1	Current paper	Elbows, wrists, knees, ankles, with tightness, swelling, reduced wrist range of motion, and a positive groove sign in the left leg and right forearm	933	3,500	MRI left tibia: very mild edema seen diffusely within the fascia	Full-thickness skin biopsy: striking expansion of the fascia by connective tissue matrix comprising collagen and mucin. Superficial inflammatory cell infiltrate permeating the fascia comprising lymphocytes and plasma cells. CD3 staining demonstrates presence of T lymphocytes, CD8+ T cells predominate	Prednisone 60 mg/day, methotrexate 20 mg/week
2	Current paper	Pitting edema of hands and feet, myalgias; subsequent skin tightness of the forearms	<20	2,400	None performed	Full-thickness skin biopsy: fibrosing stromal changes; subcutaneous, fascia, and skeletal muscle infiltration by plasma cell-rich inflammatory infiltrate with eosinophils; CD3+ staining demonstrates presence of T lymphocytes; CD4+ T cells predominate	Prednisone 60 mg/day, methotrexate 15 mg/week
3	Current paper	Swelling of volar aspect of forearms; limited knee range of motion	104	700	MRI right forearm: edema within the fascial planes of the extensor palmar compartments, muscle signal relatively maintained; mild wrist extensor and flexor tenosynovitis	None performed	Prednisone 80 mg/day, mycophenolate 3 g/day
4	Current paper	Fatigue, weight loss, extremity swelling initially; leathery texture of arms and legs; positive groove sign; reduced range of motion in fingers, wrists, elbows, shoulders, knees, and ankles		2,300	MRI pelvis: fascial edema in pelvis and proximal thighs, extensive soft tissue edema and proximal abductor muscles bilaterally	None performed	Prednisone 80 mg/day, methotrexate 15 mg/week
5	Khoja et al., 2016	Myalgia, puffiness of the face; thickened and tethered waxy skin on all limbs and abdomen	28	5,240	MRI right upper limb: marked fascial edema associated with the musculature of the arm, right chest wall involving the latissimus dorsi, serratus anterior, and pectoralis	Full-thickness skin biopsy: infiltration of dermis with a lymphoeosinophilic infiltrate with scattered eosinophils in the interstitium	Methylprednisolone 1 g/day (for treatment of coincident presumed CNS vasculitis)
6	Lidar et al., 2018	Not reported	Not reported	Not reported	PET/CT: increased uptake in soft tissues in legs	Muscle biopsy: eosinophilic fasciitis	Corticosteroid and methotrexate
7	Andrés-Lencina et al., 2018	Brownish-red plaque with significant induration and tethered waxy skin on the pubis that extended to the left anterior iliac crest region	Not reported	4,000	None performed	Full-thickness skin biopsy: dermal fibrosis with dense hyalinized collagen, extending to the subcutis and fascia. Lymphocytic perivascular infiltration was also observed with eosinophils that deepened to fascia	Prednisone 100 mg/day; methotrexate 20 mg/week (cyclosporine ineffective)

(continued)

Table 2. (continued)

Patient no.	Reference	Presentation and physical exam findings	CK, U/L	Peak absolute eosinophil count, per μ L	Imaging	Biopsy	Treatment
8	Le Tallec et al., 2019	Myalgia, diffuse skin thickening of arms and legs	WNL	4,140	MRI left thigh: abnormal linear high signal along the fasciae	Muscle biopsy: marked CD8-positive inflammatory infiltrate of the fasciae coexisting with eosinophils with an anecdotal muscle involvement, thus ruling out other diagnoses such as myositis	Corticosteroid and methotrexate
9	Toussaint et al., 2019	Myalgia, extremity edema; woody induration, peau d'orange, positive groove sign bilateral forearms	227	4,092	MRI bilateral forearms: superficial and deep fascial thickening, thickened skin, and intra-/subcutaneous edema	None performed	Prednisone 1 mg/kg/day, methotrexate
10	Rischin et al., 2018	Diffuse arthralgia and myalgia; forearms and hands with skin tightness and forearm induration, severe limitation of finger movement	WNL	600	MRI forearm: fasciitis surrounding all muscle compartments with no myositis	Left forearm biopsy: florid lymphocytic fasciitis composed of predominantly T cells and macrophages, with scattered plasma cells and perivascular cuffing by lymphocytes in the deep subcutaneous tissue and underlying fascia; CD3+ staining demonstrates presence of T lymphocytes	Prednisolone 50 mg/day, methotrexate 20 mg/week
11	Parker et al., 2018	Fatigue and myalgia; proximal muscle weakness; woody feel to skin of forearms, contracture of the left forearm flexor	75	WNL	MRI: symmetric fascial thickening and intense STIR signal centered around the muscle fascia of all thigh and calf muscle groups	Full-thickness skin-muscle biopsy: fascial and per fascicular inflammatory infiltrate with CD3 + cells; majority of myofibers showed HLA Class-I immunolabelling	Prednisolone 30 mg/day, IVIg
12	Daoussis et al., 2017	Swelling of wrists, knees, ankles, profound crepitus in all involved areas	Not reported	Not reported	MRI knee and ankle: symmetric myofasciitis with associated tenosynovitis	None performed	Methylprednisolone 12 mg/day
13	Narvaez et al., 2018	Both patients (patients 13 and 14) are described as having proximal symmetric leg weakness and stiffening of the skin of the lower extremities	Not reported	Not reported	MRI lower extremities: focal changes of myositis and fasciitis of the right gastrocnemius and soleus; subcutaneous edematous changes	None performed	NSAIDs and colchicine; drug withdrawal
14	Narvaez et al., 2018		Not reported	Not reported	MRI lower extremities: extensive changes of myositis and less marked changes of fasciitis involving the adductor muscles	None performed	Drug withdrawal
15	Bronstein et al., 2011	Clinically silent	WNL	Not reported	PET/CT: FDG-avid abdominal fasciitis	None performed	Not reported

Abbreviations: CK, creatine kinase; CNS, central nervous system; FDG, fluorodeoxyglucose; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; PET/CT, positron emission tomography/computed tomography; STIR, short tau inversion recovery; WNL, within normal limits.

the remaining six cases, the malignancy progressed in four, was stable in one, and was unknown in one.

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Patients often presented with myalgias and limb edema, sometimes with systemic symptoms such as fatigue and fever. Physical exam findings include edema, induration, a “woody” or “tethered” quality to the skin, and limitation in joint mobility.

In 11 cases, imaging studies, most commonly an extremity MRI, suggested the diagnosis. Eight patients had a tissue diagnosis usually from a full-thickness skin biopsy that showed dense infiltration of the fascia by lymphocytes and plasma cells, and variable tissue eosinophilia (Table 2). Immunohistochemistry performed in five cases demonstrated a T-cell–dominant (CD3+) infiltrate. Patients 1 and 8 had a striking predominance of CD8+ T cells, whereas patient 2 had a predominance of CD4+ T cells.

DISCUSSION

When confronted with a patient with myalgia, extremity edema, and fibrosing skin changes in the setting of a malignancy, clinicians have a variety of conditions to consider. Myositis and scleroderma can both be paraneoplastic in nature, as can EF [18–20]. In addition, cancer treatment can itself cause many of these conditions [21].

Of the 15 cases of CPI-associated EF presented here, all but 1 (Bronstein, 2011) meet the criteria for EF put forth by Pinal-Fernandez et al. [7]. Notably, as Mazori et al. report, neither the absence of peripheral eosinophilia nor the presence of muscle involvement exclude the diagnosis [22]. EF in the noncancer setting is characterized histologically by fascial thickening and fibrosis, with an inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes. Paradoxically, tissue eosinophilia may be absent [7, 22]. Light microscopic assessment is so characteristic that immunohistochemistry is rarely performed, although kappa and lambda staining is sometimes done to rule out a paraneoplastic form of EF in the setting of a plasma cell dyscrasia.

Toquet et al. demonstrate that CD8+ T cells predominate in non-CPI-associated EF and that some of these cells contain granzyme B, which might exert a direct cytotoxic effect [23]. EF in CPI-treated patients may result from prolonged CD8+ T-lymphocyte activation. Indeed, LeTallec et al. demonstrated CD8 predominance in their patient [11], and our first patient had a marked expansion of CD8+ T cells, some of which stained positive for granzyme (Fig. 3). However, this may not be the entire story, as our patient 2 had a CD4+ predominant infiltrate (Fig. 4). Pathology in CPI-induced myositis, which may share pathogenic mechanisms with EF (as demonstrated by class I

major histocompatibility complex staining in Parker et al. [14]) especially in patients with EF with muscle involvement, reveals similarly discrepant findings, with CD4 predominance in four cases [24], CD8 predominance in most of the other cases [25, 26], and one case with a CD4-to-CD8 ratio of 1:1 [27].

Peripheral blood mononuclear cell (PBMC)-derived IL-5 has also been implicated in the development of EF [28]. IL-5, which plays a crucial role in eosinophil activation, is largely produced by Th2 cells [29, 30]. PD-1 blockade in vitro has been shown to suppress Th2 responses in prostate cancer and melanoma [31], perhaps accounting for the rarity of eosinophil-related adverse events. However, tumor cells can themselves produce IL-5 [29]. In addition, IL-5 alone is not sufficient for eosinophil-lineage commitment in studies of progenitor cells [32]. Hollande et al. recently showed in a mouse model of hepatocellular carcinoma and breast cancer that tumor expression of the alarmin IL-33 was sufficient to activate eosinophil-mediated antitumor responses [33].

There has been much interest in using eosinophil counts as biomarkers of response to CPI therapy. Multiple studies show that higher baseline eosinophil counts are predictive of better overall survival in patients with melanoma treated with PD-1 blockade, CTLA-4 blockade, or a combination [34–36]. An increase in eosinophil count during treatment with ipilimumab in patients with melanoma has also been associated with an improved clinical response [37, 38]. Conversely, high eosinophil counts are associated with toxicities [39]. In an analysis of 285 patients treated with CPIs, higher eosinophil levels were associated with higher-grade (grade ≥ 3) cutaneous irAEs [40]. In the present series, eight out of nine patients with advanced melanoma had a complete response, and the remaining one patient had a partial response. For advanced cutaneous melanoma, the rate of complete response to nivolumab in clinical trials is 16% [41]. It is therefore possible that EF is a byproduct of eosinophilic antitumor activity and a good prognostic marker at least in advanced melanoma.

The treatment of EF can be challenging because of a dearth of available literature. Glucocorticoids are considered first-line therapy, and patients who do not achieve an adequate response are treated with methotrexate. In a relatively large cohort of 63 patients with EF, Wright et al. found that the mean maximum steroid dose was 51 mg and the mean duration of therapy was 18 months; 64% of patients treated with a combination of methotrexate and prednisone achieved a complete response [42]. In one retrospective study of 32 patients, the mean maximum steroid dose was 52 mg, and patients pulsed with 3 days of methylprednisolone 500–1,000 mg/day had better responses [43]. In one single-arm study, high-dose pulse methotrexate 4 mg/kg monthly was given for 5 months and all 12 patients achieved improved skin scores [44]. A variety of other immunomodulators have been used, including azathioprine, sulfasalazine, penicillamine, cyclosporine, rituximab, infliximab, tocilizumab, tofacitinib, and mycophenolate mofetil [5, 6, 45]. In the context of CPI-induced EF, therapies that preferentially inhibit T cells might make sense mechanistically, although there are no data to support this. Abatacept has not been used to treat EF, and its mechanism of action as a checkpoint agonist makes it a counterintuitive choice; however, it was recently used successfully to treat severe steroid-resistant immunotherapy-induced myocarditis

[46]. Physical therapy is a crucial component of therapy. Management requires collaboration between oncologists, rheumatologists, and dermatologists; discontinuation of the checkpoint inhibitor seems necessary.

Multiple studies show that higher baseline eosinophil counts are predictive of better overall survival in melanoma patients treated with PD-1 blockade, CTLA-4 blockade, or a combination. An increase in eosinophil count during treatment with ipilimumab in melanoma patients has also been associated with an improved clinical response. Conversely, high eosinophil counts are associated with toxicities.

CONCLUSION

Eosinophilic fasciitis should be considered in CPI-treated patients presenting with myalgias, edema, and/or skin tightening. A high peripheral absolute eosinophil count is not necessary for diagnosis. Ideally, a full-thickness skin biopsy is the best way to make an accurate diagnosis; however, this can sometimes be difficult to obtain, or there may be concern about poor wound healing. In this scenario, MRI findings can be useful when combined with the appropriate clinical scenario, as outlined by the Pinal-Fernandez criteria [7]. A high index of suspicion is necessary because if recognized early, morbidity can be limited by early intervention. Untreated, EF can lead to profound joint contractures and functional disability. Collaboration among the patient's oncologist, dermatologist, and rheumatologist is vital. Discontinuation of CPI

therapy may be necessary, and systemic steroids should be initiated promptly. If immunomodulator therapy beyond steroids is needed, methotrexate has been demonstrated to be effective in de novo EF, although the response in our series of four patients has been less impressive. Physical therapy should be encouraged, especially in patients with compromised mobility.

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DISCLOSURES

Alexander Shoushtari: Bristol-Myers Squibb, Immunocore, Castle Biosciences (C/A), Bristol-Myers Squibb, Immunocore, Xcovery (RF); **John Carrino:** Pfizer, Covera Health, Simplify Medical, Image Biopsy, Image Analysis Group (C/A); **Michael A. Postow:** Bristol-Myers Squibb, Merck, Array BioPharma, Novartis, Incyte, NewLink Genetics, Aduro (C/A), Bristol-Myers Squibb, Merck (H), RGenix, Infinity, Bristol-Myers Squibb, Merck, Array BioPharma, Novartis, AstraZeneca (RF). The other authors indicated no financial relationships.

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